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New galenic process for omeprazole containing pellets.

A production method for pellets containing Omeprazole performed with an inert core based on saccharose, starch and gum, said core covered with the micronized and sieved active substance which is in a buffered dispersion, being added with an anionic surface active agent, in order to finally recover an enteric covering in a fluidized bed with HPMC phtalate, butyl phtalate, acetone and ethyl alcohol being afterwards dried to obtain a water content of less than 1% sieved, weighted and encapsulated.

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A new production method for enteric coated pellets containing Omeprazole which is coated on an inert core in the form of pH buffered dispersion phase.

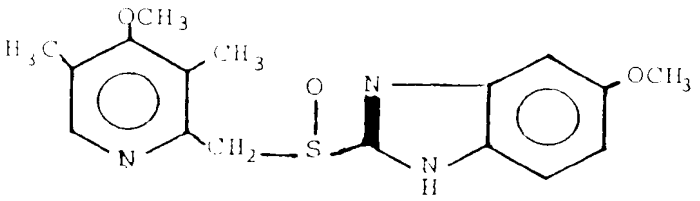
Field of invention:

The present invention is related to a new production method of a stable preparation containing Omeprazole for oral administration.

Description of invention:

Omeprazole is a potent inhibitor of gastric acid secretion. Omeprazole is a pyridine benzimidazol derivative with the following total formula $C_{17}H_{19}N_3O_3S$ and a molecular weight of 354.4.

Structure formula:



Omeprazole (1) is readily degradable in acidic enviroments, pH less than 7. Stability profile of 1 is almost the same in solid phase, and is also affected by moisture and organic solvents. The reason why oral dosage forms of Omeprazole have to be formulated as enteric coated dosage form is to protect it from acidic gastric juice. (Ref US Patent 4,786,505 Nov 22, 1988) Enteric coated pellets of Omeprazol should reasonably withstand the gastric juice but it must be dissolved rapidly in the small intestine to obtain areasonable bioavailability of course the effect. Several coating methods and materials have been used to comply the above mentioned prerequisites of Omeprazole (UK Patent GB 21 89 698).

In this patent application a new process for the preparation of aorally used hard gelatin capsule containing enteric coated Omeprazole pellets is described.

This new enteric coated pellet production process consists of the following four steps:

I.Preparation of inert core by conventional pan coating method.
II Active coating by using rotary type fluidized bed.
III Protective coating by using rotary type fluidized bed.
IV Enteric coating by using rotary type fluidized bed.

I.The contents of inert core are as following:

Saccorose **65-85%**
Corn Starch **15-25%**
Glucose **2-6%**

Particle size distrubution range is arranged to be 90% within 0.71 mm. to 0.65 mm. (in diameter) by suitable sieving. These inert pellets can also be obtained commercially.

II To obtain a rapid dispersion active (Omeprazole) substance is micronized and sieved through 150 mesh sieves.

The active substance sieved is dispersed in a buffered aqueous dispersion, at pH 7.1 ± 0.1, of a macromolecular binding agent. A anionic surface active agent (Sodium Lauryl Sulphate) is added to the aqueous phase to increase the wettability and smooth dispersion of Omeprazole.

The aqueus dispersion is sprayed on to the inert pellets in the cabin of a rotary type fluidized bed machine under appropriate process parameters.

The content of active dispersion phase for one dose hard capsule) is as following:

Omeprazole **20 mg.**
Hydroxypropil methyl cellulose **5.3 mg.**
Lactose anhydrous **8 mg.**

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L-H, [illegible] prepl, cellulose **6 mg.**
Sodium lauryl sulphate **0.5mg.**
Di[illegible]b, dreger phosphate dihydrat **0.8 mg.**
Wa[illegible] **0.21 ml.**

III A [illegible] coat[illegible] pellets have to be protected from the organic solvent which is normally used to disperse or dissolve the enteric coating material.

The thickness of this layer is experimentally determined to obtain an optimal protection during the enteric coating processes and the necessary amount of coating material per capsule (one dose) for above mentioned active coated pellets (% 100 passes through 15 mesh sieves) has been determined as following:

HPMC **3.4 mg.**
Water **0.06 ml.**

Aqueous molecular dispersion of HPMC is sprayed under appropriate process parameters onto the active coated pellets in the cabine of a rotary type fluidized bed machine and dried until the water content of the pellets is less than 1% when determined by the toluen distilation method described in USP XXII.

IV Enteric coating is performed in the same machine using appr[illegible]riate process parameters by spraying the following coating solution:

HPMC phytalate **24 mg.**
Diethyl phytalate **0.13 mg.**
Aceton **225 mg.(... ml)**
Ethyl alcohol **96 mg.(... ml)**

Finished product is sieved through 15 mesh and 20 mesh sieves. Pellets which pass through 15 mesh and are retained on 20 mesh sieves, are filled to gelatin capsules. Capsule contents are 233 mg ± 10%.

II.Protective coating phase

Machine: Glatt GPCG 60 with GRG 30
Active coated pellets: **25 kg ± 0.4**
Spray nozzle: **2 x 1.8 mn**
Nozzle position: **Tangential**
Filter type: **PB. (2% of cotton wod)**
Sieve type: **Rotor Disc.**
Inlet air Temperature: **50-60°C**
Inlet Air Rate: **700-800 m³/h**
Pumping rate: **20 rpm**
Slit width: **2 mm**
R[illegible] Sp[illegible]: **300 rpm**

III Enteric coating Phase

Machine: Glatt GPCG 60 with GRG 30
Spray nozzle: **2 x 1.8 mm**
Nozzle position: **Tangential**
Filter type: **PB2**
Sieve type: **Rotor Disc**
A[illegible] **40-50°**

Claims

capsule, characterized in that the process is performed to obtain an inert core covered with the micronized active substance to be also uniformly coated and dried after the adjusting of its granulometry, being in this way ready to be processed as capsules.

2. A production method of pellets containing Omeprazole according to the previous claim, characterized in that the inert nucleous includes a 65-85% of sacarose, 15-25% of starch and 2-66% of glucose, said nucleous being obtained by conventional means and being sieved through a mesh within 0.71 and 0.85 mm.

3. A production method according to the first claim, characterized in that the active substance is micronized and sieved through a 150 mesh to be dispersed in a buffered aqueous dispersion at pH 7.1 ± 1% with the adition of an anionic surface active agent, as for example sodium lauril sulphate.

4. A production method according to the first claim, characterized in that the active substance comprising Omeprazole, hydroxil methyl cellulose, lactose annydrous, L-hydroxy popyl-cellulose, sodium lauril sulphate, disodium hydrogen phosphate dihydrate and water is sprayed onto the inert pellets in the cabin of a rotary type fluidized bed machine.

5. A production method according to the first claim, characterized in that the enteric cover in produced in a fluidized bed with HPMC phytalate, diethyl phytalate, aceton and ethyl alcohol being afterwards dried to obtain a water content of less than 1%.

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EUROPEAN SEARCH REPORT

Application Number

EP 91 50 0066

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
Y,D	GB-A-2 189 698 (AKTIEBOLAGET HASSLE) * page 1, line 6 - line 8 * * page 2, line 25 - page 3, line 37 * * page 5 - page 6; example 2 * * page 6 - page 7; example 5 *	1,3-5	A61K9/54 A61K31/44
Y	DE-A-3 901 151 (HOECHST A.G.) * page 13; example 11 *	1,3-5	
A	EP-A-0 256 933 (ETHYPHARM) * page 2, line 61 - page 3, line 4 *	2	
A	EP-A-0 237 506 (LEJUS MEDICAL AKTIEBOLAG) * page 2, line 37 - line 43 * * page 3, line 13 - line 15 * * page 4; example 1 *	1-5	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5) A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner

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- particularly relevant if taken alone
- particularly relevant if combined with another document of the same category
- A technological background
- O non-written disclosure
- P intermediate document

- T theory or principle underlying the invention
- E earlier patent document, but published after the filing date
- D document cited in the application
- L document cited for other reasons

- & member of the same patent family, corresponding document